Molecular mechanisms of MMP9 overexpression and its role in emphysema pathogenesis of Smad3-deficient mice.

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Public Summary:
Previous studies have found that inappropriate elevation of matrix metalloproteinase-9 (MMP9) expression and activity is coincident with early onset of emphysema in Smad3-null mice. Herein, we further investigated the role of increased MMP9 in emphysema pathogenesis and the related molecular regulatory mechanisms of elevated MMP9 in Smad3-null lung. Genetic blockade of MMP9 in Smad3-null mice significantly attenuated emphysema pathology, but not hypoalveolarization during early postnatal lung development. Furthermore, Smad3 was found to be a transcription factor to positively regulate a protein deacetylase SIRT1 by binding to an AP-1 site of SIRT1 promoter. A synergistic regulatory effect on SIRT1 expression was also detected between Smad3 and c-Jun. Consistently, Smad3 knockout lung at P28 had reduced SIRT1 expression, which in turn resulted in increased acetylation of histone H3 at the transcription factor AP-1, NF-κB, and Pea3 binding sites of MMP9 promoter and increased acetylation of NF-κB. In addition, increased Pea3 expression and nuclear accumulation was also detected in Smad3-null lungs at P28. Consistently, bindings of acetylated NF-κB and Pea3 to the MMP9 promoter were elevated in Smad3-null lung. We thus propose that deficiency of Smad3 causes downregulation of SIRT1 and increased Pea3 expression/nuclear accumulation, respectively. Decreased SIRT1 activity resulted in increased acetylation of histone H3 and NF-κB. Subsequently, increased bindings of transcription factors including NF-κB and Pea3 to MMP9 promoter significantly upregulate MMP9 transcription, contributing to emphysema pathogenesis.

Scientific Abstract:
Previous studies have found that inappropriate elevation of matrix metalloproteinase-9 (MMP9) expression and activity is coincident with early onset of emphysema in Smad3-null mice. Herein, we further investigated the role of increased MMP9 in emphysema pathogenesis and the related molecular regulatory mechanisms of elevated MMP9 in Smad3-null lung. Genetic blockade of MMP9 in Smad3-null mice significantly attenuated emphysema pathology but not hypoalveolarization during early postnatal lung development. Furthermore, Smad3 was found to be a transcription factor to positively regulate a protein deacetylase sirtuin 1 (SIRT1) by binding to an AP-1 site of SIRT1 promoter. A synergistic regulatory effect on SIRT1 expression was also detected between Smad3 and c-Jun. Consistently, Smad3 knockout lung at P28 had reduced SIRT1 expression, which in turn resulted in increased acetylation of histone H3 at the transcription factor activator protein 1 (AP-1), NF-kappaB, and Pea3 binding sites of MMP9 promoter and increased acetylation of NF-kappaB. In addition, increased Pea3 expression and nuclear accumulation was also detected in Smad3-null lungs at P28. Consistently, bindings of acetylated NF-kappaB and Pea3 to the MMP9 promoter were elevated in Smad3-null lung. We thus propose that deficiency of Smad3 causes downregulation of SIRT1 and increased Pea3 expression/nuclear accumulation, respectively. Decreased SIRT1 activity resulted in increased acetylation of histone H3 and NF-kappaB. Subsequently, increased bindings of transcription factors including NF-kappaB and Pea3 to MMP9 promoter significantly upregulate MMP9 transcription, contributing to emphysema pathogenesis.